In a prospective study of the epidemiology of coronary heart disease in Framingham, Mass., biennial examinations of subjects and review of hospital and physicians' records, as well as death information, were all used to diagnose the condition. Ten-year follow-up data were used to compare these sources as to the number of cases obtained from each source, the clinical manifestations in those from each source, and the association of risk attributes with coronary heart disease for each. The findings are discussed.

AN EVALUATION OF FOLLOW-UP METHODS IN THE FRAMINGHAM HEART STUDY

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THE Framingham Heart Study has been following a sample of 5,127 adults in the town of Framingham, Mass., since 1949, chiefly to ascertain factors associated with the development of coronary heart disease (CHD). The follow-up has consisted primarily of biennial examinations of the subjects at the Study Clinic, but other sources of information such as records of hospitalizations, death certificates, medical examiner reports, and information from private physicians have also been used to determine whether or not CHD has developed.

Such a comprehensive follow-up system is expensive, in terms of both financial resources and human labor. Data from the Framingham Study, in addition to serving their primary investigative purpose, can also be used to determine whether simpler study designs would yield approximately the same results as the complete procedure used. Accordingly, an earlier investigation[1] was carried out to compare the results of cross-sectional assessment of the associations of risk attributes and CHD on individual biennial examinations, with the findings determined prospectively.

The purpose of the present investigation was to examine simpler prospective follow-up methods than the comprehensive approach used by the Framingham Study. It was assumed that the initial examination was carried out and that persons free of CHD were classified according to attributes on that examination, but that the facilities for ten-year follow-up to detect disease development were limited to each of the following: (1) only the information obtained at the Study Clinic and, more specifically, only one follow-up examination ten years after the initial examination; (2) evaluation of the available records of hospitalizations of the subjects; (3) evaluation of available information pertaining to the deaths of subjects. The specific questions asked were: (1) What proportion of the ten-year follow-up cases of CHD were diagnosed by each

of these means? (2) What was the distribution of the various manifestations of CHD as detected by these sources of data? (3) How do several important CHD risk attributes of the cases detected by the simpler means compare with those of the complete group of CHD cases?

Method

The sampling procedure and the study design used in the Framingham Heart Study and the proportion of subjects returning for each follow-up examination have been described previously.[2-4] The study population of 5,127 men and women aged 30-62 at entry and initially free of CHD have now been followed for an average of about 15 years. Complete data for this analysis was available from the first ten years of observation. During the ten-year period, 327 persons developed at least one manifestation of CHD.

Recurrent chest discomfort of a few minutes duration, precipitated by exertion or strong emotion, and relieved by rest or nitroglycerine, was regarded as *angina pectoris* if two study physicians interviewing the subject agreed on this diagnosis. If this symptom later disappeared, CHD was still considered to be present. The diagnosis of *myocardial infarction* depended on serial changes in the QRS complex of the electrocardiogram, and/or a rise in the serum glutamic oxaloacetic transaminase (SGOT) to a level of at least 60 units, the latter not attributable to other disease. While SGOT levels were only available for hospitalized patients, diagnostic electrocardiograms were obtained from private physicians and the Study Clinic as well. Some myocardial infarctions were "silent" or clinically unrecognized when they occurred.[5] *Coronary insufficiency* was diagnosed if prolonged ischemic-type chest pain was accompanied only by transient S-T segment or T wave changes in the electrocardiogram. *Sudden unexpected death* was considered diagnostic of CHD if the subject was observed to have died within an hour of the onset of symptoms and this could not reasonably be attributed to some other disease. If the terminal episode lasted longer than one hour, but the available information implied a high probability that the cause of death was CHD, this was considered to be *non-sudden death from CHD*. This diagnosis frequently utilized other clinical information in addition to that concerning the final illness.

The group of CHD cases included only the definite cases and not those considered questionable. The general approach of the study physicians reviewing the records has been to include only the clear-cut cases in the diseased group which, being relatively small, would undergo a dilution of its characteristics much more readily by false positive misclassification than would the large "normal" group by the false negatives.

For this investigation the records of the 327 subjects with definite CHD were reviewed to determine the sources of CHD diagnosis in each case. These persons were classified as to whether the diagnosis was made only at the Study Clinic, only by hospital records, only by private physician's record, only by death information, or by combinations of these sources. Thus if a person had a diagnosis of myocardial infarction made on a hospital electrocardiogram and the diagnostic changes were also present on subsequent Study Clinic tracings, he was considered to have been diagnosed both from hospital and clinic information. Further subclassification of clinic diagnosis was made according to whether the diagnostic information was obtained at the ten-year follow-up examination (Exam VI), or whether, if the subject came to Exam VI, the diagnosis of angina pectoris

had been made previously and the syndrome might have been detected if a ten-year instead of an interim two-year history of angina pectoris had been taken. Subclassification of hospital information was made according to whether the hospital was the local Framingham Union Hospital, another Massachusetts hospital, or another hospital outside of Massachusetts. When information was obtained from both the the Framingham Union Hospital and other hospitals, only the Framingham Union Hospital was listed. Information from private physicians was listed as a separate source only if there was no hospital record pertaining to the episode in question. Death information was classified according to the location of the death, containing the categories: Framingham death, death elsewhere in Massachusetts, death elsewhere in the United States and death abroad.

The CHD risk attributes that were compared were as determined at the initial examination. These included age, sex, serum cholesterol level, blood pressure, relative weight, and cigarette smoking habit. The findings of the Framingham Heart Study have generally been expressed in terms of age-adjusted incidence rates or morbidity ratios in the population classified by the attribute under study.[6,7] For purposes of this particular comparison of follow-up methods, cases classified by source of diagnosis were compared with respect to mean levels of attributes or percentages having an attribute. This permitted a more concise presentation of the results. Since the cases found by different methods showed similar mean ages, no age adjustment was made.

Results

Yield of Cases from the Different Sources of Diagnostic Information

The complete list of numbers of cases according to sources of diagnostic information is given in Table 1. Table 2 shows the total number of cases that could be diagnosed using each major source. Table 3 shows the numbers of cases that were dependent on each source as their only means of being diagnosed.

Study Clinic

The Study Clinic was a source of diagnosis of CHD in 248 (76 per cent) of the 327 cases. The ten-year follow-up examination (Exam VI), alone, contained diagnostic evidence for 156 (48 per cent of all cases). Assuming that the diagnosis of angina pectoris could have been made for those subjects developing this symptom during the first ten years, subjects who came to Exam VI but did not have angina during the two-year period prior to Exam VI, an additional 41 cases could be added to those diagnosable at the Clinic at Exam VI, yielding 197 (60 per cent) altogether (Table 2).

Almost half (151 or 46 per cent) of the cases *required* evidence obtained at the clinic for diagnosis. Of these, 95 were diagnosable at Exam VI, and if the ten-year angina pectoris history had been obtained at that examination an additional 32 would have been diagnosed, making a total of 127 (Table 1, Part A). Thus the first four follow-up examinations (Exams II-V) were required for only 56 (17 per cent) of the cases, since all other cases could be diagnosed either from Exam VI or from some nonclinic source. With the assumed ten-year angina pectoris history at Exam VI, Exams II-V were required for only 24 (7 per cent) of the cases (Table 3).

Although the clinic examinations provided the greatest yield of cases, the over-all disease incidence would have been underestimated by about one-quarter had only the clinic been used for case-finding. However, without the clinic the other sources would only have

supplied an incidence of about one-half of the total observed. The ten-year examination alone supplied sufficient evidence for most of the cases detected in the clinic. Using this one examination plus the outside sources of diagnostic information, the incidence would only have been underestimated by 17 per cent, or perhaps by as little as 7 per cent.

Table 1—Sources of diagnostic information for the 327 ten-year follow-up cases of coronary heart disease, Framingham Heart Study

Source of diagnostic information	No.	% of total
A. Study Clinic only	151	46
1. Evidence present at Exam VI	95	29
2. Exam VI diagnosis if history of former angina pectoris obtained	32	10
3. Diagnosis could not be made at Exam VI	24	7
B. Hospital only	19	6
1. Framingham Union Hospital (FUH)	17	5
2. Other Massachusetts hospitals	2	1
C. Private physician's record only	2	1
1. Framingham physician	2	1
D. Death information only	43	13
1. Death in Framingham	34	10
2. Death elsewhere in Massachusetts	6	2
3. Death elsewhere in USA	3	1
E. Study Clinic and hospital	68	21
1. FUH and diagnosis at Exam VI	52	16
2. FUH and Exam VI diagnosis with former angina pectoris history	8	2
3. FUH and diagnosis not at Exam VI	3	1
4. Other Massachusetts hospital and diagnosis at Exam VI	3	1
5. Other USA hospital and diagnosis at Exam VI	2	1
F. Study Clinic and private physician's record	5	2
1. Framingham physician and Exam VI diagnosis	4	1
2. Framingham physician and Exam VI diagnosis with former angina pectoris history	1	0
G. Study Clinic and death information	9	3
(Diagnosis could not be made at Exam VI)		
1. Death in Framingham	6	2
2. Death elsewhere in Massachusetts	1	0
3. Death elsewhere in USA	2	1
H. Hospital and death information	15	5
1. FUH and death in Framingham	11	3
2. Hospital and death both elsewhere in Massachusetts	3	1
3. FUH and death in Italy	1	0
I. Study Clinic, hospital, and death information	15	5
(Diagnosis could not be made at Exam VI)		
1. FUH and death in Framingham	12	4
2. Hospital and death both elsewhere in Massachusetts	1	0
3. FUH and death elsewhere in Massachusetts	1	0
4. FUH and death elsewhere in USA	1	0
Total	327	100

Hospital and Private Physicians' Records

Hospital records provided diagnostic information in 117 (36 per cent) of the 327 subjects with CHD. The Framingham Union Hospital (FUH) supplied

Table 2—Total cases of coronary heart disease diagnosable from each source of clinical information, ten-year follow-up, Framingham Heart Study

Source of information	Cases present	
	No.	% of all cases
All sources	327	100
Study Clinic	248	76
Study Clinic—Exam VI only	156	48
Study Clinic—Exam VI only with 10-year AP history*	197	60
Hospital records	117	36
Private physician's records	7	2
Death information	82	25

* Total cases obtainable at Exam VI if angina pectoris occurring before Exam V had been inquired about and diagnosed in subjects returning for Exam VI.

this data in 106 (91 per cent of the 117 cases) while other Massachusetts hospitals were the source of 9 (8 per cent) and other United States hospitals of 2 (2 per cent). In 19 (6 per cent), hospitals were the only source of diagnostic information.

For 7 (2 per cent) of the 327 cases, diagnostic information was available from the records of private physicians in Framingham, not counting hospital admissions. Such records were the only source in 2 cases.

Death Information

Death information was a source for diagnoses of CHD in 82 (25 per cent) of the 327 cases. As previously mentioned the diagnosis of nonsudden CHD death was not always independent or based solely on the terminal episode. The reviewing panel of physicians used all the information at its disposal to accept or reject this diagnosis. Sixty-three (77 per cent of the deaths) were in Framingham, 12 (15 per cent of deaths) were elsewhere in Massachusetts, 6 (7 per cent) were elsewhere in the United States, and 1 (1 per cent) was in Italy.

Death information was the only source of the diagnosis in 43 cases (13 per cent of all cases).

Clinical Characteristics of the Cases from Different Diagnostic Sources

Table 4 shows the clinical manifestations of CHD in 10 years in cases diagnosed in the Study Clinic, hospital, or at death as compared to those of all of the ten-year cases. The sources of diagnoses were not mutually exclusive and some subjects appeared in two or three sources.

Among patients diagnosed at the Study Clinic angina pectoris was observed in higher proportion than among all cases (83 per cent versus 64 per cent). This would be expected since virtually all diagnoses of angina were made at the clinic.* The clinic cases showed about the same proportion of myocardial infarction (42 per cent) and coronary insufficiency (13 per cent) as did all cases (38 per cent and 14 per cent respectively). Sudden and nonsudden death were less frequent in the

* Four hospital diagnoses of angina pectoris acceptable to the panel of reviewing physicians were included in this tabulation only.

Table 3—Degree of dependence on each source of diagnostic information for case-finding, ten-year follow-up, Framingham Heart Study

Source of diagnosis	Cases requiring this source for diagnosis	
	No.	% of total cases (327)
Study Clinic—all exams	151	46
Study Clinic—Exams II-V	56	17
Study Clinic—Exams II-V if had 10-year Exam VI AP history*	24	7
Hospital records	19	6
Private physician's records	2	1
Death information	43	13

* Number of cases still requiring Exam II-V for diagnosis if angina pectoris occurring before Exam V had been inquired about and diagnosed in subjects returning for Exam VI.

Table 4—Clinical manifestations of CHD cases according to source of diagnosis, ten-year follow-up, Framingham Heart Study

Manifestation	Source of diagnosis							
	All		Clinic		Hospital		Death	
	No.	%	No.	%	No.	%	No.	%
Total cases	327	100	248	100	117	100	82	100
Angina pectoris*	210	64	206	83	64	55	19	23
Nonsudden death	38	12	15	6	25	21	38	46
Sudden death	44	13	9	4	5	4	44	54
Coronary insufficiency	47	14	32	13	36	31	7	9
Myocardial infarction	123	38	104	42	89	76	27	33
CHD mortality in first 10 years	82	25	24	10	30	26	82	100

* Four hospital diagnoses of angina pectoris acceptable to the panel of reviewing physicians are included.

cases detected in the clinic (4 per cent and 6 per cent, respectively) than they were in all cases (13 per cent and 12 per cent, respectively). This is probably at least partly explained by the inability to diagnose in the clinic those whose first manifestation of CHD was fatal.

Hospital cases showed a slightly lower percentage with angina pectoris than did all cases (55 per cent versus 64 per cent). Hospital cases contained a higher proportion of nonsudden CHD death (21 per cent versus 12 per cent) and a lower proportion of sudden death (4 per cent versus 13 per cent). They exhibited coronary insufficiency (31 per cent) and myocardial infarction (76 per cent) about twice as frequently as did all cases (14 per cent and 38 per cent, respectively).

Among the 82 CHD deaths, 44 (54 per cent) were sudden, and 38 (46 per cent) were nonsudden. There was considerably less angina pectoris in this group (23 per cent) than in all patients (64 per cent), perhaps because of less opportunity for the diagnosis to be made. Myocardial infarction and coronary insufficiency were only slightly less frequent among CHD deaths (33 per cent and 9 per cent, respectively) than they were in all cases (38 per cent and 14 per cent, respectively).

The mortality from CHD within the ten-year follow-up among all cases was 25 per cent. A similar mortality of 26 per cent was noted among cases diagnosed in the hospital. The mortality of clinic cases was lower, 10 per cent.

In summary, the frequencies of clinical manifestations among cases from each source of diagnosis differed substantially in certain respects from the frequencies noted in all cases. Clinic cases showed excess angina pectoris and a lower mortality. Hospital cases showed an underrepresentation of sudden death and to a lesser extent of angina pectoris, while displaying excess myocardial infarction, coronary insufficiency, and nonsudden death. Cases derived from death information were deficient in diagnosed angina pectoris.

Risk Attributes in Cases from Various Sources

The risk attributes of the CHD cases from the different diagnostic sources are shown in Table 5. These characteristics in subjects remaining free of CHD are also shown but, because of the average age differences between

cases and non-cases, a more precise comparison between these two groups would require age adjustment. The primary purpose of this tabulation was to learn whether the risk attributes of cases from each diagnostic source differed appreciably from those of all cases.

Male Sex

Male predominance has long been recognized as characteristic of CHD. About two-thirds (67 per cent) of all of the Framingham Study CHD cases were men as compared to the 43 per cent among persons remaining free of the disease. The frequency of men (64 per cent) among the clinic-diagnosed cases was similar to that in all persons with the disease. However, hospital-detected cases and cases from death information each showed an even greater male predominance (79 per cent and 78 per cent, respectively, $p<0.05$).

Age

At entry to the study, the mean age of the cases did not vary appreciably according to the source of diagnosis. This was true for both men and women.

Blood Pressure

The mean initial systolic blood pressures in persons with CHD were approximately the same, regardless of the source of diagnosis, and the small differences noted were not consistent in men and women.

Relative Weight

In men, the mean initial relative weight in cases from each source was quite similar to that of all CHD cases. This was also true in women except those who were diagnosed at death. Women who died of CHD had a mean relative weight (105.9) which was closer to that of those remaining free

Table 5—Risk attributes of CHD cases according to diagnostic source, ten-year follow-up, Framingham Heart Study

Attributes at entry to the study	Diagnostic group				
	Free of CHD	All CHD cases	Clinic cases	Hospital cases	CHD deaths
Number of men	2,063	219	159	93	64
Number of women	2,737	108	89	24	18
Total number	4,800	327	248	117	82
Per cent men	43%	67%	64%	79%†	78%†
Mean age (men)	43.9	49.5	49.7	49.1	50.9
Mean age (women)	44.2	52.6	52.5	53.7	53.4
Mean systolic blood pressure, mm Hg (men)	137.2	149.2	147.8	152.6	156.8
Mean systolic blood pressure, mm Hg (women)	137.6	161.2	163.0	154.7	158.9
Mean relative weight* (men)	101.5	106.1	105.7	105.4	106.5
Mean relative weight* (women)	102.5	112.2	114.2	110.5	105.9
Mean serum cholesterol, mg/100cc (men)	221.7	244.2	245.4	250.0	245.3
Per cent smoking cigarettes (men)	64%	73%	72%	75%	74%

* Relative weight = per cent of median weight of those of same sex and height.
† Null hypothesis that this per cent would have occurred by chance in random selection from all CHD cases was rejected ($p<0.05$).

of CHD (102.5) than to the relative weight of all cases (112.2). However, the mean relative weight of the deaths could have differed this much from that of all of the female cases (from which they were drawn) by chance ($0.10 < p < 0.20$).

Serum Cholesterol

Since a consistent relationship of serum cholesterol to CHD had not been observed in women of all ages[6] the effects of limiting the cases to those from one diagnostic source were studied only in men. The mean initial cholesterol level in clinic cases, hospital cases, and deaths closely resembled that in all cases, and was higher than that in those remaining free of disease.

Cigarette Smoking

Because most of the CHD in women occurred in the older group in whom cigarette smoking was relatively infrequent, this attribute was best studied in men only. In men with CHD from each of the diagnostic sources the frequency of cigarette smoking closely approximated that of the entire group of cases, and was greater than that in the nonsmokers.

Discussion

Each source of diagnostic information made a contribution to detection of new coronary disease. By far the most important was the Study Clinic, without which half of the cases would have been missed, and the incidence of CHD grossly underestimated. Death information, hospital and private physicians' records each supplied information necessary to fulfill diagnostic criteria for certain individuals. Without this additional surveillance about one-fourth of the new CHD would have been missed. Thus any investigation attempting to ascertain the incidence of CHD should employ all available sources of diagnostic information. Furthermore, a complete picture of the clinical course of each person discovered to develop the disease will not be attainable without a comprehensive follow-up procedure.

It appears that follow-up examinations need not be as frequent as every two years to ensure that the Study Clinic will provide its full share of diagnostic information. This is of major importance in reducing costs since, at least with our resources and population size, biennial examinations required the continuous operation of the clinic, which has been the most costly aspect of the study. Omission of information from the second through fifth examinations, but retaining only the sixth examination (tenth year follow-up) resulted in a loss of only 17 per cent of the cases. Only 7 per cent would have been lost if one assumes that any angina pectoris occurring during the first eight, but not during the ninth or tenth years of follow-up, could have been diagnosed at the sixth examination, had it been inquired about.

Before these observations can be equated with what would have happened if the Framingham Study had been conducted with only a single ten-year follow-up examination, it must be remembered that the circumstances would have been quite different. Would, for example, the response to an invitation to return to a ten-year follow-up examination have been as favorable, had not good rapport with the subjects been fostered by the regular biennial examinations? Would the access to hospital and physicians' records have been as good had the services continuously supplied to the physicians in town by the study not been available? The study group was able to supply regular reports of the findings on subjects, as well as special tests and consultations on request. While it is not certain how great an effect on the results the lack of biennial examinations would have had, the problem of

ensuring satisfactory response to the late follow-up examination and maintaining good relations with the local hospital and medical community would have to be grappled with. Other complications might occur if a study were undertaken in a larger community in which there were several general hospitals instead of just one as has been the case in Framingham. The present findings do suggest, however, that follow-up examinations can be scheduled much less frequently than every two years with only a slight loss of CHD cases.

The differences in clinical manifestations of the cases from different diagnostic sources were what might reasonably have been expected. Clinic cases showed a relative excess of angina pectoris and were deficient in lethal manifestations. The cases diagnosed with death information were deficient in angina pectoris. Hospital-detected cases were deficient in sudden death, and in angina to some extent, and showed excess myocardial infarction, coronary insufficiency, and nonsudden death.

This distortion in the hospitalized cases might have been even more pronounced if only their hospital records had been examined. All of the information available permitted the observation and tabulation of the development of angina pectoris or the occurrence of sudden death after discharge. Similar increases in distortion would have occurred from the point of view of clinic records or death records, had these been the sole means of ascertaining manifestations in the respective groups. Thus the findings reported with respect to distribution of clinical manifestations actually underestimate the amount of bias resulting from the use of cases from a single source.

Persons with CHD in a specific clinical setting, e.g., hospital, apparently are not representative of all coronary disease present in the population. Observations on such selected groups relating to the spectrum of clinical manifestations may be applicable to other patients similarly selected but should be generalized beyond these subgroups with caution.

Nevertheless, the study of the association of several major risk factors with CHD in persons appearing in each one of the sources of diagnosis gave results that closely approximated the findings in the entire group of cases. The only exception was male predominance, which was more pronounced in the hospital cases and the CHD deaths. This is probably due to the gravitation to these diagnostic sources of cases of myocardial infarction and sudden death which are much more probable in men than in women.[6]

The over-all similarity of the findings in the variously selected cases to those of all cases with respect to age, blood pressure, cholesterol, relative weight, and cigarette smoking should be of some reassurance to the investigator who must rely on only one source of case material. He should be aware, though, of the importance of age, since older persons may not show the association of CHD with some risk factors as clearly as do younger individuals. This has been noted particularly in the case of the serum cholesterol.[1,6] It is perhaps needless to state that other risk factors not investigated herein may not show similar levels if cases from individual diagnostic sources are compared.

Summary

In a prospective investigation of the epidemiology of CHD in Framingham, Mass., biennial examinations of subjects and scrutiny of hospital and private physicians' records and death information have all been employed to diagnose CHD. The ten-year follow-up information has been used to compare these sources with regard to the numbers of cases supplied by each, the clin-

ical manifestations of the cases diagnosed from each source, and the associations of risk attributes with CHD as observed using each source.

The biennial Study Clinic examinations provided diagnostic information for three-fourths of all cases and half of the cases would have been missed without these examinations. Since, at most, a sixth of all cases were lost when all follow-up examinations except the last were ignored, it appeared that less frequent examinations might have resulted in very little underestimation of disease incidence. It is suggested, though, that frequent examinations aided in maintaining rapport and contact with both the subjects and the town physicians and without them other steps would have to be taken to ensure good follow-up.

Hospital and death information were needed for diagnosis of one-fourth of the cases. They were important in rounding out the clinical picture of CHD in the population. Each diagnostic source by itself gave its own distorted view of the distribution of clinical manifestations of CHD.

The association of CHD with age, blood pressure, serum cholesterol, relative weight, and cigarette smoking, using the cases from each source, closely resembled that found when all the cases were studied. Male predominance was exaggerated in the hospital cases and deaths. The generally good agreement noted suggests that investigators who have access to only one diagnostic source for a prospective investigation of CHD should not be discouraged from studying associations between attributes and disease even though they will only see an unrepresentative portion of the clinical spectrum of the illness.

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